

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	:	10/085,539	Confirmation No.:	9853
Applicant	:	CARLYLE, Wenda, et al.		
Filed	:	February 26, 2002		
TC/A.U.	:	1616		
Examiner	:	WEBMAN, Edward J.		
Docket No.	:	P872		
Customer No.	:	28390		
Title	:	PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA LIGAND ELUTING MEDICAL DEVICE		

Mail Stop AMENDMENT  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450


**DECLARATION OF ROBERT L. CAFFERATA**  
**UNDER 37 CFR § 1.131**

I, ROBERT L. CAFFERATA, declare the following:

1. I previously was employed by MEDTRONIC, INC., and am one of the inventors of the above-identified application.
2. I understand that in an Office Action dated 14 April 2007, the Examiner rejected Claims 1, 2, 5-7, 9, 11, and 27, of the above-identified application under 35 U.S.C. §103(a) as obvious over the combination of U.S. Patent No. 5,443,458 and International Publication No. WO 01/07066.
3. I understand that International Publication No. WO 01/07066 was filed on 19 July 2000 and published on 1 February 2001. The cover page of International Publication No. WO 01/07066 is attached as EXHIBIT A.

4. Two of my redacted laboratory notebook pages, which were prepared in the United States and witnessed by Wenda Carlyle before 1 February 2001, are attached as EXHIBIT B. The laboratory notebook pages summarize and evidence the reduction to practice of the subject matter claimed in the above-identified application. Specifically, EXHIBIT B, page 1, paragraph 1, describes a stent designed to improve the treatment of restenosis by eluting ligands of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) from the stent. EXHIBIT B, page 1, paragraphs 2 and 6, and page 2, paragraph 1, disclose that rosiglitazone is a PPAR $\gamma$  ligand and is of particular interest to elute from a stent to treat restenosis.

6. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of this application or any patents issuing thereon.

  
Robert L. Cafferata  
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Santa Rosa, CA 95405

12-18-07

Date

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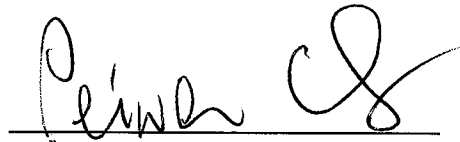
**DECLARATION OF PEIWEN CHENG**  
**UNDER 37 CFR § 1.131**

I, PEIWEN CHENG, declare the following:

1. I am one of the inventors of the above-identified application.
2. I understand that in an Office Action dated 14 April 2007, the Examiner rejected Claims 1, 2, 5-7, 9, 11, and 27, of the above-identified application under 35 U.S.C. §103(a) as obvious over the combination of U.S. Patent No. 5,443,458 and International Publication No. WO 01/07066.
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4. Two redacted pages of Robert Cafferata's laboratory notebook, which were prepared in the United States and witnessed by Wenda Carlyle before 1 February 2001, are attached as EXHIBIT B. The laboratory notebook pages summarize and evidence the reduction to practice of the subject matter claimed in the above-identified application. Specifically, EXHIBIT B, page 1, paragraph 1, describes a stent designed to improve the treatment of restenosis by eluting ligands of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) from the stent. EXHIBIT B, page 1, paragraphs 2 and 6, and page 2, paragraph 1, disclose that rosiglitazone is a PPAR $\gamma$  ligand and is of particular interest to elute from a stent to treat restenosis.

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2/25/2008  
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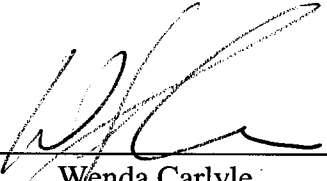
**DECLARATION OF WENDA CARLYLE**  
**UNDER 37 CFR § 1.131**

I, WENDA CARLYLE, declare the following:

1. I previously was employed by MEDTRONIC, INC., and am one of the inventors of the above-identified application.
2. I understand that in an Office Action dated 14 April 2007, the Examiner rejected Claims 1, 2, 5-7, 9, 11, and 27, of the above-identified application under 35 U.S.C. §103(a) as obvious over the combination of U.S. Patent No. 5,443,458 and International Publication No. WO 01/07066.
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\_\_\_\_\_  
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Feb 23, 2008  
Date

# **EXHIBIT A**

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number  
**WO 01/07066 A2**

(51) International Patent Classification<sup>7</sup>: **A61K 38/00**

Research Centre, Ninewells Hospital and Medical School,  
Dundee, Tayside DD1 9SY (GB).

(21) International Application Number: **PCT/EP00/06986**

(74) Agent: **RUTTER, Keith**; SmithKline Beecham, Two New  
Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(22) International Filing Date: **19 July 2000 (19.07.2000)**

(25) Filing Language: **English**

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AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): **THE  
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(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

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Roland [GB/GB]; The University of Dundee, Biomedical

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ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: **METHODS OF TREATMENT AND DRUG SCREENING METHODS**

(57) Abstract: A method of preventing or reducing foam cell development from macrophages, or removing foam cells, in a patient, the method comprising administering to the patient an effective amount of an inhibitor of PPAR $\delta$  activity. A method of preventing or treating a vascular disease associated with plaque formation and/or thrombotic blockage of the blood vessels in a patient, the method comprising administering to the patient an effective amount of an inhibitor of PPAR $\delta$  activity.

**WO 01/07066 A2**



## **EXHIBIT B**

**INVENTION:** I DISCLOSE A MODIFICATION TO A STENT DESIGNED TO IMPROVE THE TREATMENT OF RESTENOSIS BY ELUTING LIGANDS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPAR $\gamma$ ) FROM THE STENT. IN ITS SIMPLEST EMBODIMENT, A SINGLE PPAR $\gamma$  LIGAND IS ADDED TO A STENT BEFORE IMPLANTATION IN A PHARMACEUTICALLY SUFFICIENT DOSE & WITH SUFFICIENT DURATION OF ELUTION TO BLOCK THE LOCAL INCIDENCE OF RESTENOSIS AFTER STENT DEPLOYMENT IN THE BODY.

**RATIONALE FOR CHOOSING PPAR $\gamma$  LIGANDS:** PPAR $\gamma$  IS A MEMBER OF A NUCLEAR RECEPTOR SUPERFAMILY THAT IS ACTIVATED BY BINDING CERTAIN LIGANDS. THESE LIGANDS CAN BE CHOSEN FROM CERTAIN FATTY ACIDS, EICOSANOIDS AND INSULIN-SENSITIZING THIAZOLIDINEDIONES. SEVERAL PHARMACEUTICAL DRUGS ARE PART OF THIS LATTER CLASS: ROSIGLITAZONE, PIOGLITAZONE & TROGLITAZONE.

AN IMPORTANT CHARACTERISTIC OF ANTI-RESTENOTIC DRUGS AGENTS IS THEIR ABILITY TO INHIBIT SMOOTH MUSCLE CELL (SMC) PROLIFERATION. PPAR $\gamma$  LIGANDS ARE KNOWN TO INHIBIT VASCULAR SMC PROLIFERATION PROBABLY BY DIRECT INHIBITION OF CYCLIN-DEPENDENT KINASES (1, 2).

SECOND PROPERTY KEY IN AN ANTI-RESTENOTIC AGENT IS INHIBITION OF SMC MIGRATION (e.g. FROM THE MEDIA TO THE NEointIMA OF AN ARTERY). PPAR $\gamma$  LIGANDS BLOCK MIGRATION OF VASCULAR SMCs (1).

THIRD PROPERTY FOR AN ANTI-RESTENOTIC AGENT IS ITS ABILITY TO BLOCK LOCAL INVASION/ACTIVATION OF MONOCYTES & THEIR ENSUING SECRETION OF GROWTH FACTORS/CKs WHICH PRESUMABLY TRIGGER SMC ENTRY INTO THE CELL CYCLE. PPAR $\gamma$  AGONISTS INHIBIT MONOCYTE MIGRATION & PROINFLAMMATORY CYTOKINE PRODUCTION BY MONOCYTES (3). INTERESTINGLY, IT IS KNOWN THAT CERTAIN NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) LIKE SULINDAC ARE ANTI-RESTENOTIC IN CBS WITH PLAQUE-LIKE LESIONS (4). THIS COULD BE RELATED TO THE FACT THAT NSAIDs HAVE PPAR $\gamma$  AGONIST ACTIVITY AT HIGH CONCENTRATIONS (5).

RECENT CLINICAL FINDINGS DEMONSTRATE THAT PATIENTS DOSED SYSTEMICALLY WITH ROSIGLITAZONE HAVE REDUCED NEointIMAL PROLIFERATION AT SIX-MONTHS AFTER CORONARY STENT IMPLANTATION (6). UNFORTUNATELY THIS DRUG, UNDER THE TRADE NAME REZULIN, IS WITHDRAWN FROM USE IN TREATING TYPE II DIABETICS BECAUSE OF EXCESSIVE LIVER KIDNEY. SINCE PLASMA DRUG LEVELS WERE SIMILAR IN BOTH CASES, IT IS LIKELY THAT THE ANTI-RESTENOTIC EFFECTS OF SYSTEMIC TROGLITAZONE COULD ALSO LEAD TO

*[Signature]*

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DEATHS FROM LIVER TOXICITY. ONE OF THE PURPOSES OF THE PRESENT INVENTION IS TO REDUCE THE DOSE & BIODISTRIBUTION OF THIS DRUG BY ELUTING IT <sup>LOCALLY</sup> FROM A STENT WITHIN THE BODY LUMEN BEING TREATED FOR RESTENOSIS.

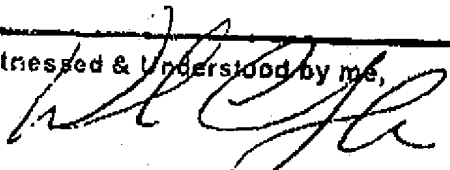
### METHODS FOR COMBINING PHARMACEUTICAL DOSAGE FORMS ONTO IMPLANTABLE DEVICES

- PRECIPITATION, COACERVATION, CRYSTALLIZATION OF DRUG ONTO THE SURFACE OF STENT (OR WEBS/CHANNELS PLACED IN THE BODY OF THE STENT AS DRUG RESERVOIR)
- BLENDING WITH POLYMERS THAT COAT THE SURFACE OF THE STENT (& ITS CHANNELS) & ACT AS A DIFFUSION-BARRIER TO CONTROL RELEASE OF DRUG
- ADDITION TO THE MATERIAL USED TO COMPOUND ERODIBLE POLYMERIC STENTS.
- CONTACT WITH CHEMICALLY REACTIVE SURFACES (FILMS) BONDED TO THE SURFACE OF THE STENT. ONE SUCH EXAMPLE WAS ANTICIPATED IN RAPID IN-SITU RELASING "DRUG IMPLANT (pp 7-11).

### REFERENCES

1. LAW, R. E. et al J Clin Invest 1996, 98(8):1897-1905.
2. WAKING, S. et al J Biol Chem 2000, 275(29):22435-41.
- 3a. KINTSCHER, U. et al Eur J. Pharmacol 2000 401(3):259-70.
- 3b. USP # 5,925,657
4. REIS, E. D. et al Proc. Natl Acad Sci USA 2000 97(23):12764-9.
5. JIANG, C. et al NATURE 1998 391(662):82-86.
6. TAKAGI, T. et al J Am Coll Cardiol 2000 36(5):1529-35.

Witnessed &amp; Understood by me,



Invented by

ROBERT L. CAFFARATI

Recorded by

1/11/01

To Page No.